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Sculpting Circuits: CRH Interneurons Modulate Neuronal Integration

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Integration of newly generated neurons into adult cell assemblies is a key mechanism for network plasticity. In this issue of *Developmental Cell*, Garcia et al. (2014) reveal a neuropeptidergic signaling mechanism by which interneurons of the olfactory system act as directors for the activity-dependent integration of adult-born granule cells.

Brain circuits are continuously sculpted through life by fluctuations in the environment, learning, and behavior. Neural plasticity occurs on a variety of levels, from subcellular changes at individual synapses during learning to large-scale alterations of entire cortical regions in response to injury. In specific brain regions, neural plasticity also occurs at the cellular level with the continuous addition and integration of neurons into preexisting circuits, a process that requires the development of completely new repertoires of synapses in the adult brain. In the olfactory bulb, for example, a class of neurons named granule cells is continuously replaced during life by new neurons born in the subventricular zone (SVZ) surrounding the lateral ventricle, one of the adult neurogenic niches. Adult-born neurons migrate through the rostral migratory stream (RMS) into the olfactory bulb, where they integrate into mature networks between 2 and 4 weeks after birth (Figures 1A and 1C). Survival of adult-born granule cells requires the establishment of reciprocal interactions with mitral cells, which serve as the main relay of olfactory information into the brain and are activated by specific sensory stimuli. It is well established that the integration of adult-born granule cells depends on neural activity (Bartolini et al., 2013), but the molecular mechanisms underlying this process remain largely unknown. In this issue of *Developmental Cell*, Garcia et al. (2014) identify GABAergic interneurons in the olfactory bulb as key cellular elements required for integration of adult-born granule cells and the neuropeptide Corticotropin-releasing hormone (CRH) as a critical modulator in this process.

Interneurons control the excitability of postsynaptic targets by releasing the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). GABAergic signaling also regulates other processes in brain development, including neurogenesis, neuronal migration, and synapse maturation (Le Magueresse and Monyer, 2013). The olfactory bulb is comprised of several layers (Figure 1B), and different populations of interneurons span several of these layers. One prominent population of GABAergic interneurons is sparsely distributed through the external plexiform layer (EPL) of the olfactory bulb, where granule cells and mitral cells establish their connections. EPL interneurons are also reciprocally connected with mitral cells, but, in contrast to granule cells, they are born at early stages and remain stable during life. Garcia and colleagues performed retrograde labeling using genetically engineered rabies virus to identify cells that provide inputs to adult-born granule neurons and discovered that these neurons receive extensive inputs from a relatively homogenous population of EPL interneurons containing CRH. Because immature granule cells receive extensive inhibitory inputs from local interneurons as they begin to integrate into the olfactory bulb network (Eyre et al., 2008; Pressler and Strowbridge, 2006), the authors reasoned that EPL interneurons expressing CRH would play an important role in this process.

Interneurons very frequently express one or more various neuropeptides in addition to GABA, and this feature is commonly used to distinguish different GABAergic interneuron populations. Neuropeptides are typically described as modulators of synaptic transmission, but they also exert a wide range of systemic effects (van den Pol, 2012). This is the case for CRH, which is best known for its role as the main regulator of neuroendocrine responses to stress in the hypothalamic-pituitary-adrenocortical axis (Bonfiglio et al., 2011). Interestingly, the main receptor mediating the function of CRH in the brain is CRHR1, and the authors elegantly demonstrate that expression of this receptor is upregulated in adult-born granule cells as they reach the olfactory bulb (Figure 1A). This led Garcia and colleagues to suggest that local CRH released by EPL interneurons may influence the integration of adult-born granule cells in the olfactory bulb.

The authors carried out loss- and gain-of-function experiments to demonstrate that CRH signaling from EPL interneurons is required for survival and functional synaptic integration of adult-born granule cells in the olfactory circuits. In particular, to rule out a systemic role of CRH on olfactory bulb maturation, the authors specifically ablated CRHR1 from adult-born granule cells by injecting Cre-expressing viruses into the RMS of mice carrying conditional loss-of-function alleles for this gene. Deletion of CRHR1 from adult-born granule cells severely prevents their integration in the olfactory bulb, as revealed by a prominent decrease in their survival. By contrast, expression of a constitutively active version of CRHR1 in adult-born granule cells enhances the formation of synapses between these cells and mitral cells. Together, these results suggest that local CRH release from EPL interneurons enhances the integration of adult-born granule cells into specific olfactory bulb circuits.

The integration of adult-born neurons into the olfactory circuit is strongly regulated by sensory input (Kelsch et al.,

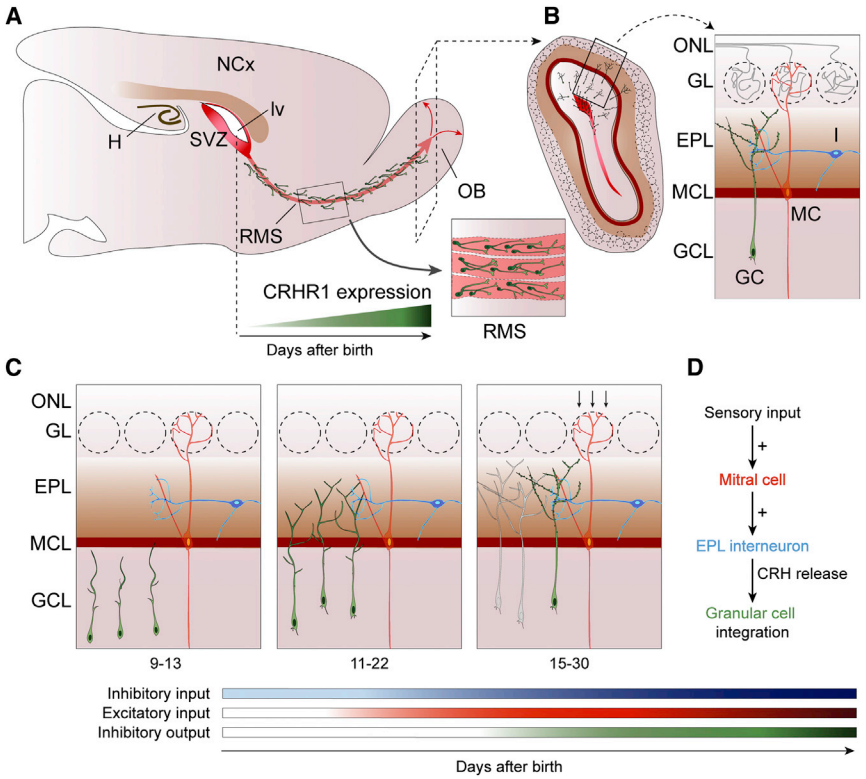

Figure 1. Corticotropin-Releasing Hormone and Circuit Integration in the Olfactory Bulb
(A) Sagittal view of the adult mouse brain illustrating generation of granule cells (GCs) in the subventricular zone (SVZ, in red) and their migration through the rostral migratory stream (RMS) into the olfactory bulb (OB). Shortly after leaving the SVZ, GCs begin expressing the type 1 receptor for Corticotropin-releasing hormone (CRHR1). (B) Coronal view of the OB depicting its laminar organization. Adult-born GCs populate the granule cell layer (GCL) and develop processes that reach the mitral cell layer (MCL) and the external plexiform layer (EPL). The inset illustrates three of the main cell types that populate these layers of the OB: GCs (in green), mitral cells (MCs, in orange) and EPL interneurons (I, in blue). MCs receive sensory information and are reciprocally connected with GCs. Interneurons receive inputs from MCs and synapse onto GCs. (C) The integration of adult-born GCs into the OB follows a highly defined sequence for the establishment of inputs and outputs and is influenced by sensory activity. (D) CRH signaling from EPL interneurons modulates integration of adult-born GCs into specific circuits. Thanks to their position in the circuit, EPL interneurons may relay the influence of sensory activity by facilitating the integration of specific GCs into networks containing active MCs. GL, glomerular layer; H, hippocampus; lv, lateral ventricle; NCx, neocortex; ONL, olfactory nerve layer.

2009; Yamaguchi and Mori, 2005). The study by Garcia et al. (2014) suggests that sensory information influences circuit assembly by activating specific mitral cells, which subsequently stimulate local EPL interneurons to release CRH and favor the integration of granule cells into these specific circuits (Figure 1D). According to this model, GABAergic interneurons act simultaneously as inhibitory regulators of the activity of mitral cells and neuromodulators of granule cells, thereby linking the survival of adult-born cells to sensory experience.

The discovery that CRH modulates synaptic development in the olfactory bulb has implications beyond the olfactory bulb. The hippocampus is a region important for learning and memory and is another site of neurogenesis in the adult brain. CRH is known to modulate synaptic plasticity during the development of hippocampal circuits (Blank et al., 2002), and the current findings raise the possibility that CRH signaling may play analogous functions in integrating new neurons into the hippocampus to modulate memory formation and recall. In addition, this study suggests that other neuropeptides may play similar roles in circuit development in other brain regions. Future work should clarify whether interneurons in other brain regions also use neuropeptides to influence network plasticity. The work from Arenkiel and colleagues has added a new meaning to the concept of neuromodulation.

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